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Alkene Cleavage

Oxidative Cleavage of Alkene C=C Bonds Using a Manganese Catalyzed Oxidation with H₂O₂ Combined with Periodate OxidationFrancesco Mecozzi,^[a] Jia Jia Dong,^[a] Davide Angelone,^[a] Wesley R. Browne,^{*,[a]} and Niek N. H. M. Eisink^{*,[b]}

Abstract: A one-pot multi-step method for the oxidative cleavage of alkenes to aldehydes/ketones under ambient conditions is described as an alternative to ozonolysis. The first step is a highly efficient manganese catalyzed epoxidation/*cis*-dihydroxylation of alkenes. This step is followed by an Fe(III) assisted ring opening of the epoxide (where necessary) to a 1,2-diol. Carbon-carbon bond cleavage is achieved by treatment of the diol with sodium periodate. The conditions used in each step are not only compatible with the subsequent step(s), but also

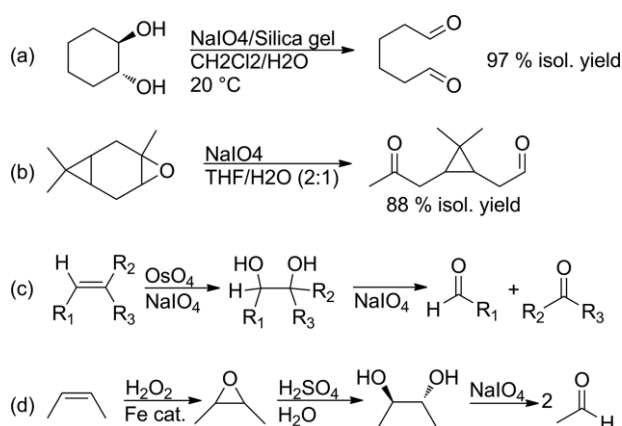
provide for increased conversion compared to the equivalent reactions carried out on the isolated intermediate compounds. The described procedure allows for carbon-carbon bond cleavage in the presence of other alkenes, oxidation sensitive moieties and other functional groups; the mild conditions (r.t.) used in all three steps make this a viable general alternative to ozonolysis and especially for use under flow or continuous batch conditions.

Introduction

Cleavage of the double bonds of alkenes to yield (di)carbonyl compounds (ketones and aldehydes) is a key reaction in synthetic organic chemistry and especially in total synthesis and medicinal chemistry.^[1] For example, ozonolysis, provides access to wide range of products controlled largely by the conditions used and the fate of the trioxolane intermediate.^[2,3] Its versatility is such that it is used widely, despite that alkene ozonolysis creates hazards in the in situ generation of O₃, and the presence of ozonides and peroxides during concentration steps. Flow chemistry^[4] can reduce the steady state concentrations of O₃, however, the latter risks are not mitigated by this approach. Furthermore, scale-up opportunities are limited by the low temperatures, typically from –78 to 0 °C^[5–8] and functional group intolerance, e.g., alkynes are converted to carboxylic acids.

A key challenge in non-ozone based methods for C=C bond cleavage is to achieve the good atom economy and selectivity that can be achieved with ozonolysis. In particular, the avoid-

ance of uncontrolled over oxidation of the products is challenging. Stepwise approaches can provide increased selectivity, as they allow greater control over the conditions in each step. For instance, initial conversion of alkenes to vic-diols, e.g. via epoxidation, can be followed by C–C bond cleavage with NaIO₄ or HIO₄, with often high selectivity and typically full conversion (Scheme 1),^[12,13] which outweighs the “single step” benefit of direct treatment of alkenes with ozone, Cr₂O₇^{2–}^[14] or MnO₄[–].^[15,16]



Scheme 1. (a) Diol C–C bond cleavage with NaIO₄, (b) C–C bond cleavage in 3-carene oxide by Binder et al.^[9] (c) The Lemieux–Johnson reaction.^[10] (d) 3-step epoxidation-ring opening-cleavage strategy developed by Klein Gebbink et al.^[11] (Fe cat = [Fe(OTf)₂(rac-BPBP)]).

One pot methods^[17] using catalytic RuCl₃ or OsO₄ in combination with either OxoneTM, NaOCl, or NaIO₄, directly exploit the ability of the oxidant to cleave the oxidation products

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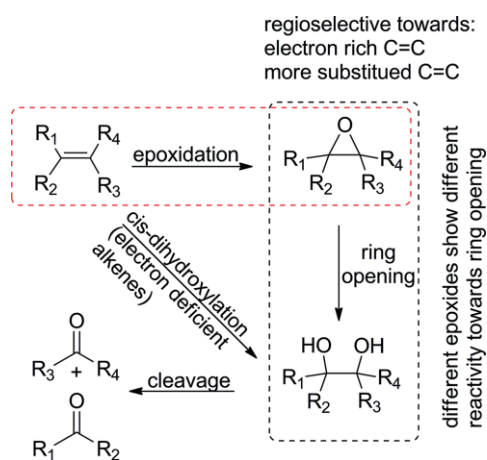
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formed by the catalytic first step.^[18–20] Lemieux and Johnson's method (Scheme 1c) for alkene double bond cleavage employs catalytic OsO_4 to form the diol intermediate and NaIO_4 both as terminal oxidant to regenerate the osmium tetroxide and to cleave the diol formed. This approach is used widely despite the cost and toxicity of OsO_4 .^[10,18,21–23] Later, RuCl_3 was used in combination with NaIO_4 or Oxone, with various solvent combinations, to give the similar transformations.^[24,25]

Recently alternative multistep approaches that replace 2nd and 3rd row transition metal-based catalysts have been developed. Ochial,^[26] Lai^[27] and co-workers have reported a multi-step one-pot cleavage of alkenes with iodosyl benzene and a manganese porphyrin catalyst, noting that epoxides were formed as intermediates in the reaction. Binder et al.^[9] reported the cleavage of epoxides to carbonyl compounds with aqueous NaIO_4 at room temperature. Klein Gebbink et al.^[11] reported a one-pot three step epoxidation-dihydroxylation-cleavage, which is equivalent to cleavage with ozone. Epoxidation with an Fe(II) catalyst and the terminal oxidant H_2O_2 was followed by sulfuric acid catalyzed ring opening and finally, cleavage of the *trans*-diol with stoichiometric NaIO_4 to yield the corresponding (di)carbonyl compounds in good to excellent yields (43 to 99 %) and selectivities (Scheme 1d). Despite limitations imposed by epoxide ring opening with sulfuric acid, the epoxidation opens up opportunities in regard to the regio- and chemo-selectivity of the system.

In a stepwise approach the selectivity towards the C=C bonds to be oxidized is governed by the epoxidation step, and hence a multistep oxidation protocol allows regioselectivity between several alkene motifs to be achieved (Scheme 2). A further point with regard to selectivity lies at the ring opening step, which has been largely neglected to date.

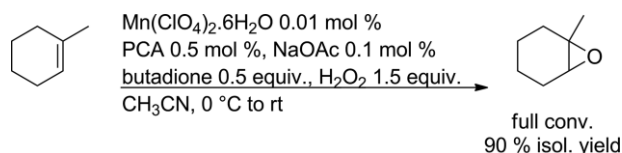


Scheme 2. One pot multistep strategy allows for the regioselectivity of the reaction to be controlled during the epoxidation and/or the epoxide ring opening steps.

A stepwise approach to the oxidative cleavage of alkene C=C bonds faces three main challenges; 1) generating the epoxide, 2) selective ring open to the diol and 3) selective oxidation of the diol. Furthermore, a "one-pot" reaction sequence necessitates compatibility between the products formed in each step and the reagents used in subsequent steps.

Here, we report a general method based on a Mn based catalyst for the oxidation of alkenes together with oxidative diol cleavage with periodate to (di)carbonyl compounds. The two/three step one-pot C=C bond cleavage reaction starts with an in situ Mn/PCA (pyridine-2-carboxylic acid) catalyzed epoxidation/*cis*-dihydroxylation with H_2O_2 as terminal oxidant. The diol is directly obtained in the oxidation with electron deficient alkenes or by the $\text{Fe}(\text{ClO}_4)_3$ mediated hydrolysis of the epoxides obtained from the oxidation of electron rich alkenes. The obtained diols are thereafter cleaved with stoichiometric NaIO_4 , yielding the corresponding (di)carbonyl compounds in high yields and selectivity. Furthermore, the regio- and chemo-selectivity in the oxidation of the various classes of alkenes is explored through the oxidation of compounds bearing multiple C=C bonds.

The conditions used in the present study for the oxidation of alkenes to their corresponding epoxide/diol was reported earlier.^[28,29] Briefly, alkene oxidation proceeds at room temperature using a combination of a Mn(II) salt, pyridine-2-carboxylic acid (PCA), (sub)stoichiometric butanedione and H_2O_2 as terminal oxidant (Scheme 3). Electron rich and electron poor alkenes are oxidized to their corresponding epoxides and diols, respectively, in high yields and selectivities and with high turnover frequencies (up to 40 s^{-1}) and numbers (up to 300 000) using this method. In the present report we show that these conditions are not only compatible with the subsequent ring opening/cleavage steps but also improve the reactions in comparison to equivalent reactions with purified intermediate products. With certain substrates, side products such as *cis*-diol and α -hydroxy ketones are observed after epoxidation. However, due to the subsequent ring opening and oxidation steps, most of these side products are converted towards the desired (di)carbonyls.

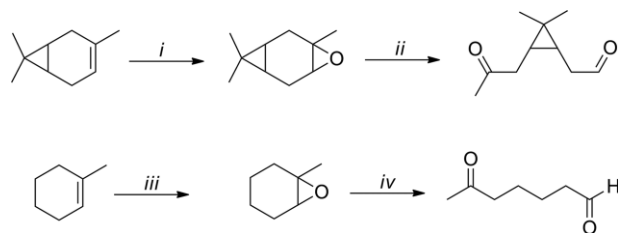


Scheme 3. Oxidation of methylcyclohexene reported by Saisaha et al.^[28,29]

Results and Discussion

Two-Step Oxidative Cleavage of Alkenes

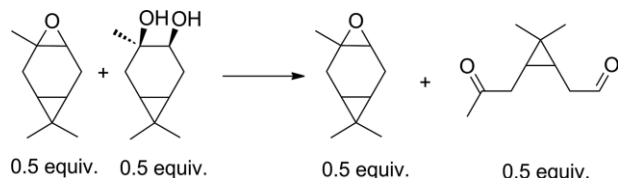
C–C bond cleavage of epoxides with aqueous NaIO_4 was reported earlier,^[9] and hence a relatively simple approach to alkene oxidative cleavage is to add NaIO_4 after the epoxidation step. With cyclic alkenes, e.g., 3-carene or methylcyclohexene (Scheme 4), epoxidation proceeded with full conversion as reported earlier.^[28] Addition of solid NaIO_4 to the reaction mixture did not result in conversion of the epoxide, in part due to poor solubility of NaIO_4 . However, dilution with water, after epoxidation, prior to adding solid NaIO_4 , provided the desired scission products as the major product (Scheme 4).



Scheme 4. One-pot two-step oxidation of 3-carene and methyl cyclohexene to the corresponding scission products via epoxides. Reaction conditions: **i**: $\text{Mn}(\text{ClO}_4)_3$ (0.02 mol-%), PCA (0.2 mol-%), butanedione (1.0 equiv.), H_2O_2 (3 equiv.), CH_3CN (0.25 M), 0 °C – r.t. 1 h **ii**: NaIO_4 (4.0 equiv.), $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (2:1, 0.17 M), r.t. 18 h **iii**: $\text{Mn}(\text{ClO}_4)_3$ (0.01 mol-%), PCA (0.1 mol-%), butanedione (0.5 equiv.), H_2O_2 (1.5 equiv.), CH_3CN (0.5 M), 0 °C – r.t. 1 h **iv**: NaIO_4 (2.0 equiv.), $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (2:1, 0.33 M), r.t. 18 h.

In acetonitrile/water, the 3-carene epoxide was converted cleanly to the desired cleavage product with 4.0 equivalents of NaIO_4 over 18 h. This result clearly indicates that the reaction conditions introduced by the first step does not hinder the subsequent oxidative cleavage. To test the influence of these reaction conditions on the oxidative cleavage of carene oxide, both in situ generated epoxide as isolated epoxide were subjected to the oxidative cleavage (1.0 equivalent of NaIO_4 in acetonitrile/water, 2:1, 0.16 M for 18 h). Analysis by ^1H NMR spectroscopy after 18 h proved that the in situ prepared carene epoxide formed $2.5 \times$ more product than the isolated epoxide. This indicates that the reaction conditions from the first step, most likely the acetic acid formed from butanedione, is highly advantageous in regard to the subsequent periodate oxidation. The conditions are not only compatible but also are complementary to each other.

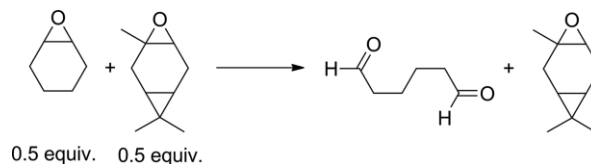
In the examples described thus far, the epoxidation step takes place under mildly acidic (acetic acid) conditions, however, the addition of periodate and water does not result in rapid epoxide ring opening. A competition reaction between 3-carene-oxide and diol with equimolar amounts of NaIO_4 illustrates that ring opening is the rate-limiting step (Scheme 5). The vic-diol was oxidized rapidly and preferentially leaving the epoxide untouched. These data confirm that direct oxidation of the epoxide by periodate is not kinetically competent and the difference in reactivity opens opportunities for selectivity in cleavage between epoxides.



Scheme 5. Selective oxidation of the 3-carene diol in the presence of the 3-carene oxide. Reaction conditions: NaIO_4 (0.5 equiv.), r.t. $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (2:1, 0.5 M), 18 h.

This kinetically determined selectivity is exemplified in the kinetic attrition of a mixture of cyclohexene and 3-carene epoxides. Treating this mixture with 0.5 equivalent of NaIO_4 left the 3-carene oxide relatively untouched while the cyclohexene ox-

ide was nearly fully consumed (Scheme 6) indicating that indeed the more readily opened epoxide is not only selectively opened but also subsequently cleaved to the dicarbonyl product.

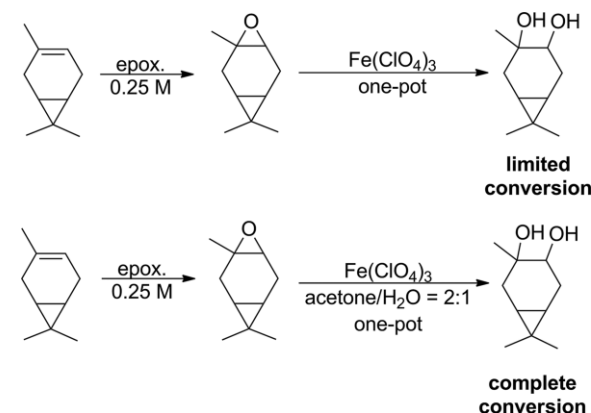


Scheme 6. Selective oxidation of cyclohexene oxide in the presence of 3-carene oxide. Reaction conditions: NaIO_4 (0.5 equiv.), r.t. $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (1:1, 0.5 M), 18 h.

Ring Opening of Epoxides with $\text{Fe}(\text{ClO}_4)_3$

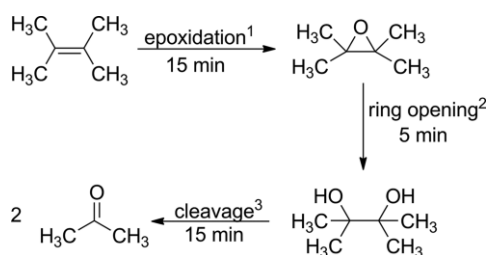
The epoxide ring opening is typically accelerated using hard acids such as H_2SO_4 or BF_3 etherate, however these are not desirable in regard to achieving a broad functional group tolerance. Iron(III) salts were considered as a viable alternative to these hard acids, as they have been shown earlier to catalyze the ring opening of epoxides in the presence of various nucleophiles;^[30–33] in particular in alcohols.^[34,35] First attempts to catalyze the ring opening of the epoxide product formed in acetonitrile with $\text{Fe}(\text{ClO}_4)_3$ were unsuccessful, possibly due to formation of the stable complex $[\text{Fe}(\text{CH}_3\text{CN})_6]^{2+}$.

The flexibility of the $\text{Mn}(\text{II})/\text{PCA}$ system in terms of solvent, opens up opportunities to achieve the ring opening step in acetone.^[28] Epoxidation of 3-carene in acetone proceeded in full conversion within 10 min (determined by ^1H -NMR spectroscopy). Addition of solid $\text{Fe}(\text{ClO}_4)_3$ to solutions lead to only limited conversion towards the desired diol (Scheme 7). Since in the current protocol, NaIO_4 is added with water, addition of aqueous $\text{Fe}(\text{ClO}_4)_3$ to perform ring opening was explored and indeed, with water, the diol products were obtained within 3 h at room temperature. 1.0 mol-% $\text{Fe}(\text{ClO}_4)_3$ in a 2:1 acetone/water ratio proved to be optimal for both achieving high conversion and maintaining a homogeneous solution.



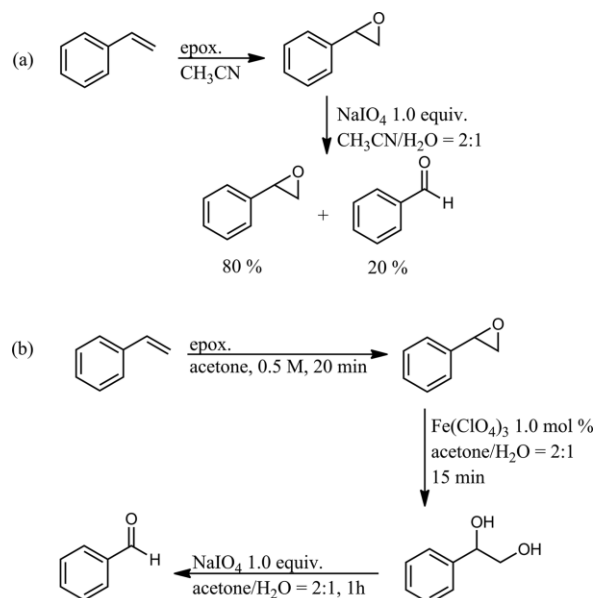
Scheme 7. Summary of ring opening reactions. Reaction conditions: **Epoxidation**: $\text{Mn}(\text{ClO}_4)_3$ (0.02 mol-%), PCA (0.2 mol-%), butanedione (1.0 equiv.), H_2O_2 (3 equiv.), CH_3CN (0.25 M), 0 °C – r.t. 1 h **$\text{Fe}(\text{ClO}_4)_3$** : $\text{Fe}(\text{ClO}_4)_3$ (1.0 mol-%), in CH_3CN (0.25 M) or $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (2:1, 0.17 M), r.t. 18 h.

The compatibility of the reagents used, and by-products formed (e.g., acetic acid) was examined using a one-pot three-step reaction. Epoxidation of 2,3-dimethyl-2-butene in $(\text{CD}_3)_2\text{CO}$ (Scheme 8) was followed by ring opening to the corresponding diol with $\text{Fe}(\text{ClO}_4)_3$ in H_2O and subsequent cleavage to acetone with 1.0 equiv. of NaIO_4 . The reaction was monitored by Raman spectroscopy and $^1\text{H-NMR}$ and all three steps went to completion with high selectivity within 1 h at room temperature. The reaction proceeds with full conversion and selectivity to the expected product (acetone).



Scheme 8. One-pot three step oxidation of the 2,3-dimethyl-2-butene at room temperature. 1) $\text{Mn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ 0.01 mol-%, PCA 0.5 mol-%, NaOAc 1.0 mol-%, butanedione 0.5 equiv., H_2O_2 1.5 equiv., $(\text{CD}_3)_2\text{CO}$, 0.5 M substrate, 15 min; 2) $\text{Fe}(\text{ClO}_4)_3$ 1.0 mol-%, $(\text{CD}_3)_2\text{CO}/\text{H}_2\text{O}$ (2:1, v/v), 5 min; 3) 1 equiv. NaIO_4 , $(\text{CD}_3)_2\text{CO}/\text{H}_2\text{O}$ (2:1, v/v), 15 min.

The same reactions were attempted on aryl-alkenes considering that reactivity of aryl-alkenes is often distinctly different to aliphatic alkenes, especially in regard to the stability of their



Scheme 9. (a) Two step cleavage of styrene oxide. (b) 3 step one pot oxidation of styrene. Epoxidation: $\text{Mn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ 0.01 mol-%, PCA 0.5 mol-%, NaOAc 1.0 mol-%, butanedione 0.5 equiv., H_2O_2 1.5 equiv., acetone, 0.5 M substrate, 30 min; $\text{Fe}(\text{ClO}_4)_3$: $\text{Fe}(\text{ClO}_4)_3$ 1.0 mol-%, acetone/ H_2O (2:1, v/v), 15 min; cleavage: 1 equiv. NaIO_4 , acetone/ H_2O (2:1, v/v), 30 min.

epoxide products. Addition of periodate in water to the formed styrene epoxide, resulted in only 20 % conversion, Scheme 9a. In contrast, the one-pot three step approach in which the ep-

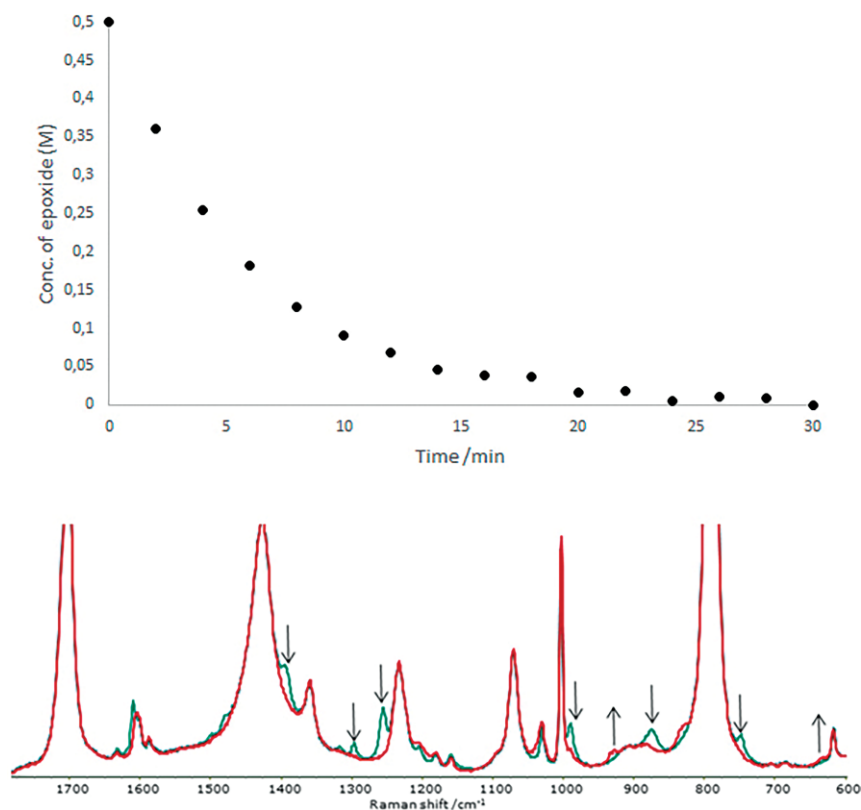


Figure 1. In-line monitoring of the ring opening of styrene oxide by Raman spectroscopy showing complete ring opening within 20 min. Top: decay of Raman band of epoxide at 1254 cm^{-1} , bottom: Raman spectra before and after ring opening.

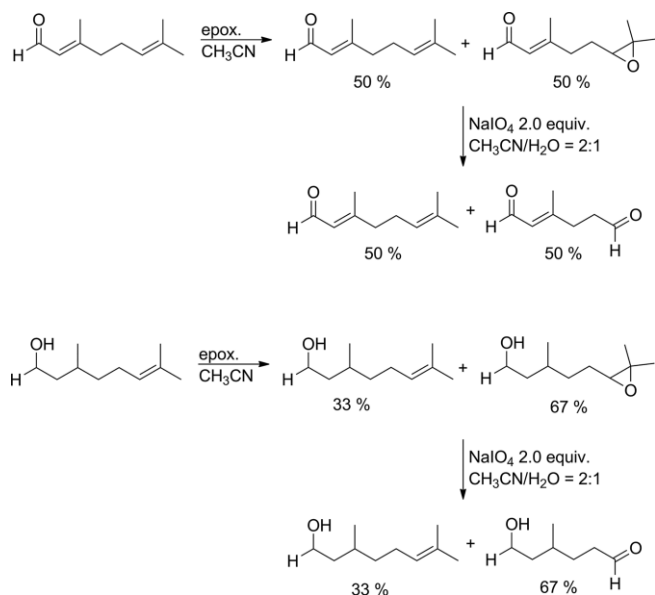
oxidation of styrene with H_2O_2 was followed by ring opening and oxidation periodate provided the desired product within 1 h at room temperature.

Indeed, the epoxidation was complete within a few minutes and the subsequent iron(III) catalyzed ring opening of the epoxide was complete within 20 min (Figure 1 and Scheme 9). The subsequent oxidative C–C bond cleavage with periodate/water was complete within 1 h. The short reaction time required for the Lewis acid catalyzed ring-opening of the styrene oxide opened a facile pathway for the C–C bond cleavage of aromatic substrates and new possibilities for the chemoselectivity of the system.

The compatibility of the reaction conditions for epoxidation with the ring opening step is exemplified by subjecting isolated styrene oxide to the $\text{Fe}(\text{ClO}_4)_3$ catalyzed ring opening. The ring opening was proceeded in 75 % conversion after 15 min while the in situ generated epoxide was fully converted within the same time.

Functional Group Tolerance of the System

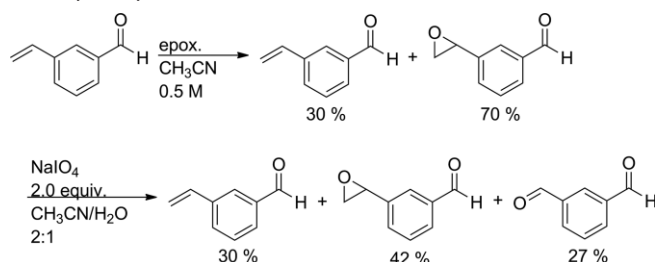
The limits to the selectivity that could be achieved with the one pot three step reaction were explored in the partial epoxidation of both citral and citronellol. Partial epoxidation allowed for the sensitivity of the unreacted alkene to the conditions of the subsequent steps to be evaluated. Oxidation with 2.0 equiv. of NaIO_4 (with 50 % water by volume) resulted in selective conversion of the epoxide to the desired aldehyde, with full recovery of remaining starting material (Scheme 10). These data confirm that neither terminal alcohols, trisubstituted, nor α,β -unsaturated alkenes are sensitive to the cleavage conditions of the final step. Furthermore, it demonstrates that double bond selec-



Scheme 10. One-pot two step C=C bond cleavage of citral and citronellol. *Epoxidation*: $\text{Mn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ 0.01 mol-%, PCA 0.5 mol-%, NaOAc 1.0 mol-%, butanedione 0.5 equiv., H_2O_2 1.5 equiv., acetonitrile, 0.5 M substrate, 30 min; *cleavage*: 2 equiv. NaIO_4 , acetonitrile/ H_2O (2:1, v/v), 3 h.

tivity in the epoxidation step can be used to control the overall selectivity of C=C bond cleavage.

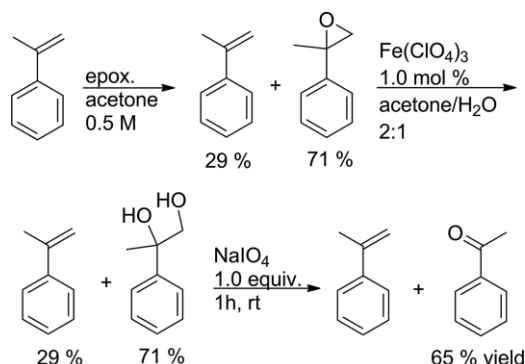
Similar results were obtained with 3-vinyl benzaldehyde. In a one-pot 2-step reaction (i.e. without deliberate ring opening of the epoxide product) epoxidation of the alkene was allowed to proceed up to ~70 % conversion. Subsequent partial oxidation of the resulting epoxide to 1,3-benzene-dialdehyde was then performed. Both reactions were done without complete conversion to monitor the stability of the various functional groups to the reaction conditions. It can be concluded that the aldehyde functionality was preserved in both steps, i.e. the aldehyde did not react in the oxidation of the alkene nor with NaIO_4 . Furthermore, the alkene moiety was unaffected by the subsequent periodate oxidation. (Scheme 11).



Scheme 11. Partial conversion of the 3-vinyl benzaldehyde to its epoxide and subsequently dialdehyde. *Epoxidation*: $\text{Mn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ 0.01 mol-%, PCA 0.5 mol-%, NaOAc 1.0 mol-%, butanedione 0.5 equiv., H_2O_2 1.5 equiv., acetonitrile, 0.5 M substrate, 60 min; *cleavage*: 2 equiv. NaIO_4 , acetonitrile/ H_2O (2:1, v/v), 3 h.

Scope of the Reaction

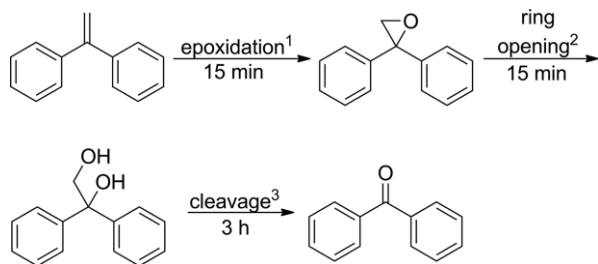
α -Methyl styrene was converted to acetophenone under the same reaction conditions as used for the oxidation of styrene and isolated by column chromatography in 65 % yield, with an overall reaction time of 2 h, for the three steps. It is important to note that the epoxidation step proceeded with 71 % conversion, indicating that the subsequent two steps were essentially quantitative and selective towards formation of the desired product. (Scheme 12).



Scheme 12. 3 step one-pot C=C bond cleavage of α -methyl styrene. *Epoxidation*: $\text{Mn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ 0.01 mol-%, PCA 0.5 mol-%, NaOAc 1.0 mol-%, butanedione 0.5 equiv., H_2O_2 1.5 equiv., acetonitrile, 0.5 M substrate, 30 min; *cleavage*: 1 equiv. NaIO_4 , acetonitrile/ H_2O (2:1, v/v), 1 h.

In the case of the epoxidation of diphenyl ethylene initially low conversion was observed under the standard reaction con-

ditions. This was overcome^[29] by reducing the concentration of the starting material to 0.25 M (Scheme 13).

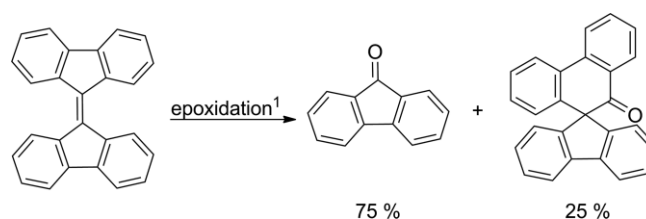


Scheme 13. 3 step one-pot C=C bond cleavage of diphenyl ethylene. 1) $\text{Mn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ 0.02 mol-%, PCA 1.0 mol-%, NaOAc 2.0 mol-%, butanedione 1.0 equiv., H_2O_2 3.0 equiv., acetone, substrate 0.25 M, r.t., 15 min; 2) $\text{Fe}(\text{ClO}_4)_3$ 1.0 mol-%, acetone/ H_2O (2:1 v/v), r.t., 5 min; 3) NaIO_4 1.2 equiv., acetone/ H_2O (2:1, v/v), r.t., 3 h.

Subsequent ring opening was rapid (< 1 h), while the C–C bond cleavage step was complete using a slight excess of NaIO_4 (3 h). A basic workup yielded the desired product in almost quantitative yield and high selectivity (Figure 2).

Although relatively insoluble, bisfluorene was also submitted to the three step procedure. Oxidation took place under the same conditions but with an 8-fold decrease in substrate concentration compared with that used typically, with ca. 75 % of the ketone product together with the pinacol rearranged product (ca. 25 %) (Scheme 14). Notably, analysis after the first (epoxidation) step revealed that the desired scission product (fluorenone) was already present. Epoxidation of the highly strained alkene present in bisfluorene, is likely to be followed by ring opening to the diol and, in the presence of excess peroxide, to further oxidation leading to cleavage. Indeed, the out-

come of the first step is not changed by the subsequent steps. To the best of our knowledge, the epoxide is not described in the literature and the diol has been shown to undergo photochemical rearrangements to the ketone and rearranged product in similar ratios to that observed here.^[36,37] We surmise that the reaction either proceeds via a carbocation intermediate or formation of the diol.



Scheme 14. Direct C=C bond cleavage of bisfluorene. 1) $\text{Mn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ 0.08 mol-%, PCA 4.0 mol-%, NaOAc 8.0 mol-%, butanedione 4.0 equiv., H_2O_2 12.0 equiv., acetone 0.0625 M, r.t., 30 min.

Although providing for facile epoxide ring opening with $\text{Fe}(\text{III})$ salts, the use of acetone in combination with H_2O_2 , raises a safety issue, due to the possible formation of explosive organic peroxides. For larger scale reactions, the use of an in-flow epoxidation-ring opening arrangement for the oxidation of the alkenes is desirable. The epoxidation step was performed in-flow using a syringe pump and simple HPLC tubing and mixer: the substrate and the reagents, in one syringe, were mixed continuously with a solution of H_2O_2 . The addition of the reaction mixture to aqueous $\text{Fe}(\text{III})(\text{ClO}_4)_3$ yielded the corresponding diol quantitatively, and subsequent addition of sodium periodate achieved bond cleavage. Using this approach, styrene was converted to benzaldehyde (vide supra) at 5 mmol scale also.

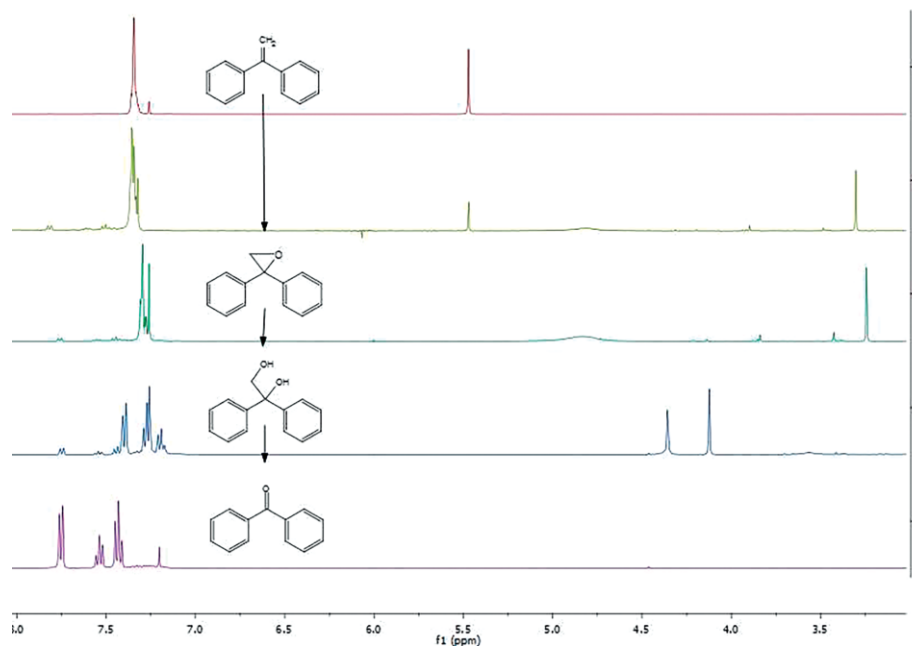


Figure 2. ^1H -NMR spectra of (A) 1,1-diphenyl-ethene, and crude products after (B) epoxidation (incomplete conversion, 0.5 M), (C) epoxidation (complete conversion, 0.25 M), (D) ring opening and (E) cleavage reactions, (respectively).

Conclusions

We report an alternative protocol to ozonolysis that overcomes several of the limitations imposed by ozonolysis in the cleavage of C=C bonds to ketone and aldehydes. All steps are carried under ambient conditions with off-the-shelf reagents in the presence of water and air in contrast to the “classic” ozonolysis conditions (e.g., -78°C) and avoids the formation of potentially hazardous intermediates such as trioxolane intermediates. The approach provides for useful selectivity both between double bonds and with regard to other functional group. For instance, the lack of reactivity of alkynes, primary alcohols and aldehydes reported earlier for the Mn/PCA catalyzed oxidation with H_2O_2 opens up application of this C=C bond cleavage approach to alkenes bearing these functional groups. The selectivity of the present method comes from both the first oxidation step: The Mn/PCA based epoxidation/syn-dihydroxylation is both selective and specific towards electron rich double bonds over α,β -unsaturated double bonds; and the epoxide ring opening step. The C–C bond cleavage can be performed directly on the epoxide with between 2 and 4 equiv. of periodate, however, if the epoxidation is carried out in acetone, facile ring opening to the diol with $\text{Fe}(\text{ClO}_4)_3$ proceeds relatively quickly (depending on substrate) and can be followed by cleavage with only one equiv. of NaIO_4 , with overall reaction times of less than 4 h.

Importantly, the regioselectivity can be controlled through the ring opening step also, as different epoxides show markedly different reactivity towards the conditions used for ring opening with iron(III) perchlorate or direct oxidation with NaIO_4 .

Furthermore, not only are all described steps compatible with each other, but they complement each other also. When performing the reaction steps in consecutively in a one-pot manner, higher conversions are obtained compared to the isolated counter parts.

Experimental Section

See the Supporting Information for experimental details regarding reaction details and characterization.

General Procedure for Substrate Oxidation

Epoxidation

The substrate (1 mmol) was added to a 0.5 mL solution of $\text{Mn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ (0.2 mM in either acetonitrile or acetone, 0.1 μmol , 0.01 mol-%) and 0.5 mL solution of picolinic acid (10 mM in either acetonitrile or acetone, 5 μmol , 0.5 mol-%). 17 μL NaOAc (0.6 M in H_2O , 10 μmol , 1 mol-%), 43.5 μL butanedione (0.5 mmol, 0.5 equiv.) and either acetonitrile or acetone were added to give a final volume of 2 mL and a final concentration of the substrate of 0.5 M (for less reactive substrates the amount of starting material is reduced by half to give a final concentration of 0.25 M). The solution was stirred in an ice/water bath before addition of 85 μL H_2O_2 (50 wt.-%, 1.5 mmol, 1.5 equiv.). Conversion was monitored either directly by Raman spectroscopy or indirectly by ^1H NMR spectroscopy (by dilution of a part of the reaction mixture in CD_3CN or by directly diluting the sample in CDCl_3).

One pot epoxide ring opening

When epoxidation (in acetone) was complete, $\text{Fe}(\text{ClO}_4)_3$ (3.5 mg, 10 μmol , 1.0 mol-%) was added with water (half the volume of

the reaction mixture); the reaction was monitored either directly by Raman spectroscopy or indirectly by ^1H NMR spectroscopy (a small sample of reaction was shaken with 1 mL brine and 1 mL CDCl_3 , and the organic layer was used to record the ^1H NMR spectrum).

Diol and epoxide C–C bond cleavage

Reaction mixture containing the diol (or the epoxide in acetonitrile) was added NaIO_4 (214 mg, 1.0 mmol, 1.0 equiv.). Water (half the volume of the reaction mixture) was added in the case of direct epoxide opening in acetonitrile, in these cases the amount of NaIO_4 is increased up to 2–4 equiv. The reaction was monitored indirectly by ^1H NMR spectroscopy (a small sample of reaction was shaken with 1 mL brine and 1 mL CDCl_3 , and the organic layer was used to record the ^1H NMR spectrum). Product isolation involved addition of brine (10 mL) and extraction with dichloromethane (3×10 mL). The combined organic layers were washed with brine, dried with Na_2SO_4 (anhydrous), filtered and the dichloromethane was removed in vacuo to yield the crude product.

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